Depression Physician's Manual

VNS Therapy™ Pulse
Model 102 Generator

and

VNS Therapy™ Pulse Duo
Model 102R Generator

March 2004

Caution: U.S. federal law restricts this device to sale by or on the order of a physician.

REF 26-0005-6300/1

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1-D. BRIEF DEVICE DESCRIPTION

Please refer to Section 1 in the epilepsy part of this manual for a brief description of the components of the VNS Therapy System, compatibility, and symbols and definitions used in this manual.

2-D. INTENDED USE / INDICATIONS

The VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or recurrent depression* for patients over the age of 18 who are experiencing a major depressive episode that has not had an adequate response to two or more adequate antidepressant treatments*.

* See glossary for a definition of terms.

3-D. CONTRAINDICATIONS

⚠ The VNS Therapy System cannot be used in patients after a bilateral or left cervical vagotomy.

⚠ Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (hereafter referred to as diathermy) on patients implanted with a VNS Therapy System. Diagnostic ultrasound is not included in this contraindication.

Energy delivered by diathermy may be concentrated into or reflected by implanted products such as the VNS Therapy System. This concentration or reflection of energy may cause heating.

Testing indicates that diathermy can cause heating of the VNS Therapy System well above temperatures required for tissue destruction. The heating of the VNS Therapy System resulting from diathermy can cause temporary or permanent nerve or tissue or vascular damage. This damage may result in pain or dis comfort, loss of vocal cord function, or even possibly death if there is damage to blood vessels.

Because diathermy can concentrate or reflect its energy off any size-implanted object, the hazard of heating is possible when any portion of the VNS Therapy System remains implanted, including just a small portion of the Lead or electrode. Injury or damage can occur during diathermy treatment whether the VNS Therapy System is turned “ON” or “OFF”.

Diathermy is further prohibited because it may also damage the VNS Therapy System components resulting in loss of therapy, requiring additional surgery for system explantation and replacement. All risks associated with surgery or loss of therapy (loss of seizure control) would then be applicable.

Advise your patients to inform all their health care professionals that they should not be exposed to diathermy treatment.

4-D. WARNINGS

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy System physician's manuals.

⚠ **Unapproved uses**

The **safety and efficacy** of the VNS Therapy System has not been established for uses not covered in the "Intended Use/Indications" section of this manual.

⚠ **Unspecified nerve, muscle, or tissue stimulation**

The safety and efficacy of the VNS Therapy System have not been established for stimulation of the **right vagus nerve** or of any other nerve, muscle, or tissue.

⚠ **Excessive stimulation**

Note: Use of the Magnet to activate stimulation is not recommended for patients with depression. The Magnet Mode output current should remain at 0.0mA for patients with depression.

Excessive stimulation at an excess duty cycle (that is, one that occurs when ON time is greater than OFF time) has resulted in degenerative nerve damage in laboratory animals. An excess duty cycle can be produced by continuous or frequent magnet activation (? 8 hours), as determined by animal studies. Cyberonics recommends against stimulation at these combinations of ranges.

⚠ **Device manipulation**

Patients who manipulate the Pulse Generator and Lead through the skin (Twiddler's Syndrome) may damage

or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve.

⚠ **Swallowing difficulties**

Aspiration may result from the increased swallowing difficulties reported by some patients during stimulation. Patients with **pre-existing swallowing difficulties** are at greater risk for aspiration.

⚠ **Device malfunction**

Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage and other associated problems. Patients should be instructed to use the Magnet to stop stimulation if they suspect a malfunction, and then to contact their physician immediately for further evaluation. Prompt surgical intervention may be required if a malfunction occurs.

⚠ **Dysfunctional cardiac conduction systems**

Susceptible patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been studied as part of controlled clinical trials to establish the safety of VNS Therapy System treatment in these patients. Evaluation by a cardiologist is recommended if the family history, patient history, or electrocardiogram suggests an abnormal cardiac conduction pathway. Serum electrolytes, magnesium, and calcium should be documented before implantation. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated.

⚠ **Obstructive sleep apnea**

Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Cyberonics recommends care when treating patients with pre-existing OSA. Lowering stimulus frequency or prolonging OFF time may prevent exacerbation of OSA.

⚠ **VNS Therapy device is not curative**

Physicians should warn patients that VNS Therapy has not been proven to be a cure for depression.

5-D. PRECAUTIONS

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy System physician's manuals.

⚠ **Laryngeal irritation** may result from stimulation. **Patients who smoke** may have an increased risk of laryngeal irritation.

⚠ **Dyspnea** may result from stimulation. **Patients with chronic obstructive pulmonary disease** may have an increased risk of dyspnea.

⚠ It is important to follow recommended implantation procedures and intraoperative product testing described in this manual. During the intraoperative Lead Test, infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate is encountered during a Lead Test or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

Additionally, postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. If a patient has experienced asystole, severe bradycardia (heart rate < 40 bpm) or a clinically significant change in heart rate during a Lead Test at the time of initial device implantation, the patient should be placed on a cardiac monitor during initiation of stimulation.

The safety of this therapy has not been systematically established for patients experiencing bradycardia or asystole during VNS Therapy System implantation.

⚠ **Reversal of Lead polarity has been associated with an increased chance of bradycardia** in animal studies. It is important to make sure that the Lead connector pins are correctly inserted (white marker band/serial number to + connection) into the Lead receptacle(s).

⚠ **Do not program the VNS Therapy System to an ON or periodic stimulation treatment for at least 14 days after the initial or replacement implantation.** Failure to observe this precaution may result in patient discomfort or adverse events.

⚠ **Resetting the Pulse Generator** turns the device OFF (output current = 0.0 mA), and all device history information is lost. The device history information should be printed out before resetting.

⚠ **Do not use frequencies of 5 Hz or below for long-term stimulation.** Because these frequencies generate an electromagnetic trigger signal, their use results in excessive battery depletion of the implanted Pulse Generator and, therefore, should be used for short periods of time only.

⚠ It is important to follow **infection control procedures**. Infections related to any implanted device are difficult to treat and may require that the device be explanted. Cyberonics recommends that the patient be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the operation.

Cyberonics recommends frequent irrigation of both incision sites with generous amo unts of bacitracin or equivalent solution prior to closure. (To minimize scarring, these incisions should be closed with cosmetic closure techniques.) Also, antibiotics should be administered postoperatively at the discretion of the physician.

⚠ The VNS Therapy System is indicated for use only in stimulating the **left vagus nerve** in the neck area inside the carotid sheath.

⚠ The VNS Therapy System is indicated for use only in stimulating the **left vagus nerve below where the superior and inferior cervical cardiac branches separate from the vagus nerve.**

⚠ **Physicians who implant the VNS Therapy System** should be experienced performing surgery in the carotid sheath; physicians should be familiar with vagal anatomy, particularly the cardiac branches; and they should be trained in the surgical technique relating to implantation of the VNS Therapy System. See Section 12.2 in the epilepsy part of this manual.

⚠ A **neck brace** can be used by the patient for the first week to help ensure proper Lead stabilization.

⚠ **Appropriate physician training** is very important.

- ✍✍ **Prescribing physicians** should be experienced in the diagnosis and treatment of depression and should be familiar with the programming and use of the VNS Therapy System.
- ✍✍ **Physicians who implant the VNS Therapy System** should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to implantation of the VNS Therapy System. (See Section 12.2 in the epilepsy part of this manual for more information.)

5.1-D. Sterilization, Storage, and Handling

Please refer to Section 5.1 in the epilepsy part of this manual for information on sterilization, storage, and handling of the VNS Therapy System.

5.2-D. Lead Evaluation and Connection

Please refer to Section 5.2 in the epilepsy part of this manual for information on evaluating and connecting the Lead component of the VNS Therapy System.

5.3-D. Environmental and Medical Therapy Hazards

Please refer to Section 5.3 in the epilepsy part of this manual for information on environmental and medical therapy hazards that may affect the VNS Therapy System, devices that may be affected by the VNS Therapy System, and guidance for disposal of the Pulse Generator.

6-D. ADVERSE EVENTS

The safety profile of VNS Therapy observed in the feasibility (D-01) and pivotal (D-02) studies is consistent with the known safety profile of VNS Therapy that has emerged from the epilepsy clinical trials and more than 56,000 patient-years of commercial use. The adjunctive use of VNS Therapy among patients with treatment-resistant, chronic or recurrent depression appears to be associated with similar adverse effects and safety risks as its use among patients with treatment-refractory epilepsy.

It is important to note that subjects often had comorbid illnesses and almost all study subjects were also receiving antidepressant and other drugs that could have contributed to these events.

6.1-D. Serious Adverse Events (SAEs)

6.1.1-D. Low Number of SAEs Reflects Safety of VNS Therapy

During the pivotal (D-02) study, 13 SAEs were considered related to the implant procedure (wound infection, asystole, bradycardia, syncope, abnormal thinking, vocal cord paralysis [two reports], aspiration pneumonia, voice alteration, device site reaction [two reports], acute renal failure, and urinary retention). Investigators did not report any SAE to be related to stimulation. During the long-term phase of the pivotal (D-02) study, nine SAEs were considered at least possibly related to stimulation (sudden death of unknown cause, syncope [2 reports], dizziness, a manic depressive reaction in a subject with bipolar disorder, hemorrhage GI, vocal cord paralysis, paresthesia, and an incident of worsening depression for which the investigator considered VNS Therapy a possible but unlikely contributor). These relatively few reports of SAEs attributable to VNS Therapy implantation or stimulation reflect the relative safety of VNS Therapy.

6.1.2-D. No Direct Role of VNS Therapy in Deaths

Four deaths occurred during the pivotal (D-02) study: one after the subject had given consent, but before the subject was implanted; the second, a suicide; the third, a death of unknown cause; and the fourth, a subject who developed multi-organ failure. No direct role of VNS Therapy is evident in any of these deaths.

6.1.3-D. Unanticipated Adverse Device Effects

Two events in the pivotal (D-02) study met criteria for an unanticipated adverse device effect (UADE)—see Glossary for definition. Both these events were non-specific complications of surgery related to the implant procedure and occurred before stimulation began. One UADE was an episode of acute renal failure thought to be secondary to antibiotic administration, and the other was an episode of altered mental status thought to be due to perioperative narcotic administration.

6.2-D. Safety Considerations Specific to Depressed Patients

Two specific safety concerns in the use of all antidepressant therapies are the precipitation of manic or hypomanic episodes and the possible effect of antidepressant therapy on suicidal ideation and behavior.

6.2.1-D. Antidepressant Treatments and Manic or Hypomanic Reaction

Although patients with bipolar disorder experience manic episodes as the cardinal feature of their disorder, effective antidepressant therapies themselves can occasionally precipitate a manic or hypomanic episode. Antidepressant therapies can also occasionally precipitate a manic or hypomanic episode in patients without a prior history of mania who are being treated for a major depressive episode.

6.2.1.1-D. Manic Reactions Within Expected Range

In the pivotal (D-02) study, six hypomanic or manic reactions were identified according to DSM IV criteria and the Young Mania Rating Scale (YMRS). Five were observed in subjects with a known history of prior hypomanic or manic episodes. Considering that lithium therapy, the standard drug used to

control mania, had not been successful for these subjects with bipolar disorders, the incidence of hypomanic or manic reactions in the pivotal (D-02) study seems to be well within the expected range.

6.2.2-D. 56% of VNS Therapy Subjects Showed Decreased Suicidal Ideation Scores

At 12 months of VNS Therapy, 90% of the subjects in the pivotal (D-02) study showed either improvement (56%) or no change (34%) in their scores on item 3 of the $HRSD_{24}$, which measures suicidal ideation.

6.3-D. High Rate of Subject Continuation

6.3.1-D. Low Rate of Discontinuations Because of Adverse Events

In the feasibility (D-01) study, no discontinuations were related to adverse events attributed to VNS Therapy or the implant procedure. By the time all continuing subjects in the pivotal (D-02) study had at least 1 year of VNS Therapy, 3% (8/235) of the subjects had discontinued VNS Therapy for an adverse event-related reason. The reasons for these eight discontinuations included one case each of suicide, implant-related infection necessitating device removal, hoarseness, lightheadedness, post-operative pain, chest and arm pain, sudden death (of unknown cause), and worsening depression (reported by the investigator as an adverse event rather than as lack of efficacy).

This low rate of discontinuation attributed to adverse events demonstrates that VNS Therapy is very well tolerated in subjects with treatment-resistant depression.

6.3.2-D. Implant-Related Adverse Events

Because all eligible study subjects in the pivotal (D-02) study were implanted with the VNS Therapy System device, no control was available to assess whether an adverse event was related to the surgery. Investigators, therefore, determined which adverse events were related to implantation. The events reported as related to implantation and occurring in at least 10% of the subjects who received VNS Therapy System implants in the pivotal (D-02) study were device site pain, device site reaction, incision pain, dysphagia, hypesthesia, pharyngitis, voice alteration, and incision site reaction. Most of the individual incidences of these events resolved within 30 days.

Hypesthesia (generally described as a localized numbness) and voice alteration, however, tended to be more persistent in some individuals. For example, in 17 of 25 reports of implantation-related hypesthesia, the event continued beyond 3 months. Hypesthesia would be an expected side effect of nerve injury during surgery. The persistence of voice alteration in some subjects is difficult to assess because it could represent surgical injury to the innervation of the larynx, but vagus nerve stimulation itself can cause voice alteration.

6.4-D. AE Relationship to VNS Therapy

Investigators determined whether an adverse event (AE) was possibly, probably, or definitely related to implantation of or stimulation by the VNS Therapy Pulse Generator and Lead.

6.5-D. AEs Related to Implantation

Tables D-1 and D-2 list implantation-related adverse events.

Table D-1. Implantation-Related Adverse Events Occurring in ?5% of Subjects During the Acute Phase of the Pivotal (D-02) Study

Body System	D-02 Acute Phase Incidence of Surgery-Related AEs (N=235)
Body as a Whole	
Incision Pain	36%
Device Site Pain	23%
Device Site Reaction	14%
Headache	8%
Neck Pain	7%
Pain	7%
Cardiovascular System	
None ?5% Reported	
Digestive System	
Dysphagia	11%
Nausea	9%
Endocrine System	
None ?5% Reported	
Hemic and Lymphatic System	
None ?5% Reported	
Metabolic and Nutritional Disorders	
None ?5% Reported	
Musculoskeletal	
None ?5% Reported	
Nervous System	
Hypesthesia	11%
Paresthesia	6%
Respiratory System	
Voice Alteration	33%
Pharyngitis	13%
Dyspnea	9%
Cough Increased	6%
Skin and Appendages	

Body System	D-02 Acute Phase Incidence of Surgery-Related AEs (N=235)
Incision Site Reaction	29%
Special Senses	
None>5% Reported	
Urogenital	
None >5% Reported	

Table D-2. Implantation-related Adverse Events < 5% Acute Phase-Pivotal (D-02) study

Body System
Body as a Whole
Abdominal Pain, Allergic Reaction, Anaphylactic Reaction, Asthenia, Back Pain, Chest Pain, Chills, Fever, Infection, Injection Site Pain, Neck Rigidity, Photosensitivity Reaction, Surgical Injury, Viral Infection, Wound Infection
Cardiovascular System
Arrhythmia, Asystole, Bradycardia, Hemorrhage, Migraine, Palpitation, Syncope, Tachycardia
Digestive System
Anorexia, Constipation, Diarrhea, Dyspepsia, Flatulence, Gastrointestinal Disorder, Vomiting
Endocrine System
Thyroid Disorder
Hemic and Lymphatic System
Ecchymosis, Lymphadenopathy
Metabolic and Nutritional Disorders
Edema, Hyperglycemia, Peripheral Edema
Musculoskeletal
Arthralgia, Joint Disorder, Myalgia, Myasthenia
Nervous System
Abnormal Dreams, Agitation, Ataxia, Dizziness, Hypertonia, Insomnia, Nervousness, Neuralgia, Neuropathy, Thinking Abnormal, Tremor, Vasodilatation, Vocal Cord Paralysis

Body System
Respiratory System
Aspiration Pneumonia, Asthma, Atelectasis, Bronchitis, Hiccup, Hypoxia, Laryngismus, Laryngitis, Lung Disorder, Respiratory Disorder, Rhinitis, Sinusitis, Sputum Increased
Skin and Appendages
Application Site Reaction, Maculopapular Rash, Pruritus, Rash, Sweating
Special Senses
Ear Disorder, Ear Pain, Tinnitus
Urogenital
Acute Kidney Failure, Dysuria, Metrorrhagia, Urinary Retention

6.5.1-D. Stimulation-Related Adverse Events

The investigators determined that seven events occurring at a frequency of 10% or greater among subjects assigned to the treatment group were stimulation-related: voice alteration (55%), cough increased (24%), dyspnea (19%), neck pain (16%), dysphagia (13%), laryngismus (11%), and paresthesia (10%). After 60 days, subjects were no longer reporting most of the seven events. Laryngismus (7 of 13) and voice alteration (53 of 68), however, tended to be more persistent with subjects continuing to report the event for more than 3 months.

Tables D-3 and D-4 list stimulation-related adverse events that occurred during the acute phase of the pivotal (D-02) study.

Table D-3. Stimulation-Related Adverse Events ?5% Treatment Versus Control, Acute Phase - Pivotal (D-02) study

Body System	D-02 Treatment (N=119)	D-02 Sham-control * (N=116)
Body as a Whole		
Incision Pain	6 (5%)	3 (3%)
Neck Pain	19 (16%)	1 (<1%)
Cardiovascular System		
None ?5%		
Digestive System		
Dysphagia	15 (13%)	0 (0%)
Nausea	8 (7%)	1 (<1%)
Endocrine System		
None ?5%		
Hemic and Lymphatic System		
None ?5%		
Metabolic & Nutritional Disorders		
None ?5%		
Musculoskeletal System		
None ?5%		
Nervous System		
Paresthesia	12 (10%)	3 (3%)

Body System	D-02	D-02 Sham-control * (N=116)
Respiratory System		
Cough Increased	28 (24%)	2 (2%)
Dyspnea	23 (19%)	2 (2%)
Laryngitis	13 (11%)	0 (0%)
Pharyngitis	9 (8%)	1 (<1%)
Voice Alteration	65 (55%)	3 (3%)
Skin and Appendages		
None ?5%		
Special Senses		
None ?5%		
Urogenital		
None ?5%		

*****Note: These subjects were not receiving stimulation during this phase.

Table D-4. Stimulation-related Adverse Events <5% in the Treatment Group, Acute Phase-Pivotal (D-02) Study

Body System
Body as a Whole
Asthenia, Chest Pain, Device Site Pain, Device Site Reaction, Headache, Neck Rigidity, Pain
Cardiovascular System
Migraine, Palpitation, Postural Hypotension, Syncope, Tachycardia
Digestive System
Anorexia, Constipation, Diarrhea, Dyspepsia, Eructation, Flatulence, Increased Appetite, Vomiting
Endocrine System
None reported
Hemic and Lymphatic System
None reported
Metabolic and Nutritional Disorders
Weight Gain
Musculoskeletal
Myalgia, Myasthenia
Nervous System
Abnormal Dreams, Agitation, Depression, Dizziness, Emotional Lability, Hypertonia, Hypesthesia, Insomnia, Manic Reaction, Nervousness, Sleep Disorder, Somnolence, Twitching, Vasodilatation
Respiratory System
Asthma, Hiccup, Respiratory Disorder, Rhinitis
Skin and Appendages
Incision Site Reaction
Special Senses
Ear Pain, Tinnitus
Urogenital
Amenorrhea

6.5.2-D. Stimulation-related Events, Long-term Phase

Tables D-5 and D-6 list adverse events that occurred at an incidence of ?5% and <5%, respectively. These adverse events were observed over quarters of stimulation. Subjects are counted only once within each body system, preferred descriptive term, eg, neck pain, nausea, or pharyngitis, and time interval.

Table D-5. Percentage of Stimulation-related Adverse Events ?5% By Quarters of Stimulation - Pivotal (D-02) Study

Body System	3 Mos. N=232	6 Mos. N=225	9 Mos. N=218	12 Mos. N=209
Body as a Whole				
Neck Pain	16%	11%	14%	13%
Pain	6%	6%	5%	6%
Headache	5%	4%	4%	4%
Cardiovascular System				
None ?5% Reported				
Digestive System				
Dysphagia	13%	8%	7%	4%
Nausea	6%	2%	2%	2%
Endocrine System				
None ?5% Reported				
Hemic and Lymphatic System				
None ?5% Reported				
Metabolic & Nutritional Disorders				
None ?5% Reported				
Musculoskeletal System				
None ?5% Reported				
Nervous System				
Paresthesia	11%	7%	4%	4%
Respiratory System				
Voice Alteration	58%	60%	57%	54%
Cough Increased	24%	9%	7%	6%
Dyspnea	14%	16%	15%	16%
Laryngismus	10%	8%	7%	5%
Pharyngitis	6%	4%	4%	5%
Skin and Appendages				
None ?5% Reported				
Special Senses				
None ?5% Reported				
Urogenital				
None ?5% Reported				

Table D-6. Stimulation-Related Adverse Events, Long-term Phase, <5% Pivotal (D-02) Study

Body System
Body as a Whole
Abdominal Pain, Asthenia, Chest Pain, Device Site Pain, Device Site Reaction, Flu Syndrome, Incision Pain, Neck Rigidity, Viral Infection
Cardiovascular System
Bradycardia, Hypotension, Migraine, Palpitation, Postural Hypotension, Syncope, Tachycardia
Digestive System
Anorexia, Colitis, Constipation, Diarrhea, Dyspepsia, Eructation, Flatulence, Gastritis, Gastrointestinal Disorder, Increased Appetite, Vomiting
Endocrine System
None reported
Hemic and Lymphatic System
None reported
Metabolic and Nutritional Disorders
Weight Gain, Weight Loss
Musculoskeletal
Athralgia, Joint Disorder, Myalgia
Nervous System
Abnormal Dreams, Agitation, Amnesia, Anxiety, Confusion, Depression, Dizziness, Dry Mouth, Emotional Lability, Hypertension, Hypertonia, Hypesthesia, Insomnia, Manic Reaction, Manic Depressive Reaction, Nervousness, Sleep Disorder, Somnolence, Speech Disorder, Thinking Abnormal, Tremor, Twitching, Vasodilatation, Vocal Cord Paralysis
Respiratory System
Asthma, Hiccup, Respiratory Disorder, Rhinitis, Stridor
Skin and Appendages
Incision Site Reaction, Sweating
Special Senses
Amblyopia, Deafness, Ear Pain, Eye Pain, Tinnitus
Urogenital
Amenorrhea, Menstrual Disorder

6.6-D. High Continuation Rate

Of the 295 subjects implanted during both the feasibility (D-01) and pivotal studies (D-02), 270 subjects (92%) were still receiving VNS Therapy at 12 months.

6.6.1-D. Device safety

The VNS Therapy System performed according to its labeling. Most device issues were communication difficulties easily resolved by repositioning the programming wand or replacing the programming wand batteries. One high lead impedance occurred requiring replacement; a lead break due to fatigue at the electrode bifurcation was noted. Most device complaints were resolved on the day of initial complaint.

6.6.2-D. Most Adverse Events Decreased Over Time

Subjects who reported adverse events during the first 3 months of stimulation and continued to report those adverse events were monitored by 3-month intervals. The largest decreases were noted between the first and second quarters of stimulation. The most notable exception was voice alteration. During the first quarter, 135 of 209 subjects (65%) reported voice alteration. Of those 135 subjects, 90 continued to report it during the fourth quarter of stimulation.

6.6.3-D. Very Few Late-emerging Adverse Events

After the first 3 months of stimulation, the incidence of first-reported adverse events did not exceed 1.3% of total study subjects for any event.

6.6.4-D. Adverse Events Classification

Investigators rated adverse events as mild, moderate, or severe according to the protocol definitions: mild events were

transient and easily tolerated by the subject; moderate events caused discomfort and interrupted usual activities; severe events caused considerable interference with the subject's usual activities.

6.6.5-D. Most Adverse Events Rated Mild or Moderate

Most adverse events for the feasibility (D-01) study and pivotal (D-02) study were mild or moderate. Because the pivotal (D-02) study included a sham-control group, further analysis of severity rating was performed. At 3 months of VNS Therapy, there were 280 (43%) adverse events that were categorized as mild, 293 (45%) as moderate, and 73 (11%) as severe in the pivotal (D-02) study sham-control group. The pivotal (D-02) study treatment group had 360 (47%) adverse events categorized as mild, 349 (45%) as moderate, and 61 (8%) as severe. The frequency of events rated as severe during the pivotal (D-02) study was slightly less in the treatment group than in the sham-control group. Stimulation did not seem to impose a higher risk for severe events.

6.7-D. Conclusion

VNS Therapy is a tolerable therapy (92% continuation rate at 1 year D-01/D-02) that is also safe. The adverse and serious adverse events reported in the depression studies were similar to those in epilepsy studies. VNS Therapy is a safe and tolerable therapy for persons with treatment-resistant depression.

7-D. CLINICAL STUDIES OF DEPRESSION

7.1-D. Safety and efficacy

Results of clinical trials demonstrated the safety and efficacy of VNS Therapy for treatment-resistant depression. For most subjects, antidepressant effectiveness improved over time and was sustained long term. After 12 months of VNS Therapy, more than one in two subjects received a meaningful clinical benefit and one in six was essentially free of depressive symptoms. Of the subjects who showed an initial benefit, 73% maintained the benefit after 12 months. Almost 50% of subjects who had no benefit at 3 months had meaningful benefit after 12 months. The treatment was well tolerated as evidenced by 90% of the study participants remaining in the study after 1 year. Most side effects, typically related to stimulation, were rated as mild or moderate and many lessened with time.

7.2-D. Mechanism of Action

Although the mechanism of action is not completely understood, several studies have shown that VNS Therapy influences neurotransmitters and brain structures thought to be involved in depression.[1,2,3,4] In addition, brain imaging studies

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[1] Henry, TR, Votaw JR, Pennell PB, et al. *Acute* blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. *Neurology*. 1999;52:1166-1173.

[2] Krahl SE, Clark KB, Smith DC, Browning RA. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia.* 1998;39:709-714.

[3] Chae J-H, Nahas Z, Lomarev M, Denslow S, Lorberbaum JP, Bohning DE, George MS. A review of functional neuroimaging studies of vagus nerve stimulation (VNS). *J Psychiatric Res.* 2003;37:443-455.

[4] Jobe PC, Dailey JW, Wernicke JF. A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders. *Crit Rev Neurobiol.* 1999;13:317-356.

have shown that VNS Therapy modulates blood flow or metabolism in many areas of the brain that are implicated in neuropsychiatric disorders.[3]

Reports of improved mood among patients receiving VNS Therapy for treatment of epilepsy prompted studies among subjects with treatment-resistant depression. During the clinical trials that evaluated VNS Therapy as a treatment for epilepsy, some subjects experienced an improvement in mood. In some cases these improvements seemed to exceed what would be expected based on the amount of improvement observed in the subjects' epilepsy.

7.3-D. Feasibility (D-01) Study

The primary efficacy measure in the open-label feasibility (D-01) study was the percent of subjects responding (response was defined as a 50% or greater improvement in the $HSRD_{28}$ score). Of the 59 subjects with evaluable data, 18 (31%) responded at acute study exit, which was 12 weeks after implantation. Observation of subjects continued. After 1 year of VNS Therapy, 25 of 55 subjects (45%) responded, and after 2 years, 18 of 42 (43%) responded. One in six subjects reached remission (defined as $HRSD_{28}$ scores less than 10) after 1 and 2 years of treatment. Other measures of depressive symptoms (CGI, MADRS, BDI, IDS-SR) and quality of life (MOS-36) supported the $HRSD_{28}$ scores.

7.4-D. Pivotal (D-02) Study

The pivotal (D-02) study of VNS Therapy consisted of both an acute and a long-term phase to collect data regarding the safety and efficacy of VNS Therapy as an adjunctive treatment for persons with chronic or recurrent treatment-resistant depression.

7.4.1-D. Pivotal Study, Acute Phase (D-02 Acute)

The acute phase was a 12-week (after implantation), double-blind, randomized, parallel-group sham treatment-controlled, multi-center study. Subjects were assigned randomly to either the treatment (stimulation) group or control (sham) group and results of these two groups were compared. All subjects in both groups meeting the eligibility criteria for participation in the study were implanted with the VNS Therapy Pulse Generator and VNS Therapy Lead. The VNS Therapy System remained OFF for 2 weeks after implantation to allow for recovery from surgery. Most subjects in the pivotal (D-02) study were being treated with one or more antidepressant medications at the time of enrollment. Medications were to remain constant at the pre-implant baseline dosages throughout the acute phase for both the treatment and sham-control groups.

Sham Control: Sham-control group subjects were treated the same as the treatment group, except that the output current of the device remained at 0.0 mA so that it did not deliver stimulation during the acute phase.

Treatment Group: Two weeks after implant, stimulation was initiated for the treatment group. Over the next 2 weeks, parameters were adjusted to patient tolerance, then remained constant for the rest of the acute phase (8 weeks). Decreases in stimulation parameters were permitted to accommodate patient tolerance.

7.5-D. Pivotal (D-02) Study, Long-term Phase

All pivotal (D-02) study subjects who completed the acute phase were eligible to continue into the long-term extension phase, during which all subjects received active VNS Therapy. During the first 10 weeks of the extension phase, sham-control subjects (also referred to as the delayed treatment group for the long-term phase), received stimulation parameter adjustments. Weekly or every other week clinic visits and assessments were identical to those experienced by the treatment group during the acute phase. Otherwise, the protocol specified monthly clinic visits for both groups through 12 months of active VNS Therapy. Various assessments, including depression ratings, were performed throughout this period. During the long-term extension phase, investigational site programmers were allowed to adjust stimulation parameters as clinically indicated. Additionally, concomitant antidepressant treatments could be added, removed, or adjusted as clinically indicated.

7.5.1-D. Comparative Assessments

The comparative (D-04) study was a long-term, observational, prospective study to collect data regarding usual standard-of-care for treatment-resistant chronic or recurrent depression in persons who were experiencing a major depressive episode at the time of admission. Clinical (depression assessments) and quality of life outcomes were assessed at baseline, 3, 6, 9, and 12 months.

7.5.1.1-D. Concomitant Therapies

Subjects enrolled in the comparative (D-04) study met the same enrollment criteria regarding chronicity or recurrence of depression, previous treatment failures, and severity of depression as subjects in the pivotal (D-02) study. Because the

study was observational in nature, the protocol did not specify therapies for the treatment of depression; rather the physician managing the study subject's depression selected therapy according to clinical judgment. Thus antidepressant therapy in the comparative (D-04) study comprised "standard of care" treatment (also known as "treatment as usual"). The entire range of treatment options available for the comparative (D-04) study subjects was also available to the pivotal (D-02) study subjects as concomitant treatment to their VNS Therapy. Thus subjects in both the long-term pivotal (D-02) extension and the comparative (D-04) study received standard of care treatment; however, only the pivotal (D-02) study subjects received VNS Therapy.

The comparative (D-04) study was conducted at 13 investigational sites, 12 of which were also pivotal (D-02) study sites. The similarities in the key inclusion criteria and study sites provide a basis to expect that the demographic and disease characteristics of both groups would be comparable, which was confirmed by the results of the analyses conducted to examine the comparability. These subjects provided a comparison group for the pivotal (D-02) study subjects at 12 months.

Table D-7. Description of Subjects in Pivotal (D-02) and Comparative (D-04) Studies

	Pivotal (D-02) Study	Comparative (D-04) Study
Number of subjects (evaluable population)	205	124
Mean age (years)	46.3	45.5
Number of females	131 (64%)	85 (69%)
Diagnosis: Unipolar	185 (90%)	109 (88%)
Diagnosis: Bipolar	20 (10%)	15 (12%)
Mean duration of illness (years)	25.5	25.8
Mean duration of this depressive episode (months)	49.9	68.6
Subjects who previously received ECT during lifetime	108 (53%)	32 (26%)
Subjects who previously received ECT during current major depressive episode	72 (35%)	15 (12%)
Number of failed adequate trials of antidepressants during this current major depressive episode	3.5	3.5
Mean age at onset of first symptoms of depression, mania, hypomania (years)	21.8	20.8
Mean number of previous hospital admissions for mood disorders in lifetime	2.7	2.1

7.6-D. Data Analysis

7.6.1-D. Pivotal (D-02) study

The primary efficacy variable for both the acute and the long-term phases of the pivotal (D-02) study was the Hamilton Rating Scale for Depression-24 item ($HRSD_{24}$). For the acute-phase analysis, the $HRSD_{24}$ response rate (percentage of subjects with a ?50% improvement from baseline to 3 months, acute phase exit) was compared between the treatment and the sham-control groups. For the long-term phase, a linear regression model was used to assess the changes in $HRSD_{24}$ raw scores. Secondary efficacy analyses included 1) between-group comparisons of the Inventory of Depressive Symptomatology-Self Report (IDS-SR), 2) the Clinical Global Impression (CGI), and 3) Medical Outcome Survey 36-Item Short Form Health Survey (MOS SF-36).

7.6.2-D. Comparative (D-04) Study

The primary efficacy variable for the D-02 and D-04 comparative analysis was the IDS-SR (raw scores). Multiple assessments with the IDS-SR allowed use of a linear regression model for the analysis. The $HRSD_{24}$ was used as a secondary assessment variable to analyze differences in response rates and raw score changes between subjects in the pivotal (D-02) and comparative (D-04) studies. Subjects in the comparative (D-04) study were assessed with the $HRSD_{24}$ only at baseline and 12 months.

Secondary analyses included IDS-SR average change, IDS-SR response, IDS-SR complete response, IDS-SR sustained response, $HRSD_{24}$ average change, and $HRSD_{24}$ response. Other secondary analyses included the CGI.

7.6.3-D. Propensity Scores

To reduce selection bias, propensity scores, defined as the conditional probability of being treated given the covariates, were used to balance the covariates between the two groups. Propensity scores provide a scalar summary of the covariate (eg, age, number of prior depressive episodes, etc) information. They are not limited by traditional methods of adjustment, which can only use a limited number of covariates for adjustment. Propensity scores were calculated for the pivotal (D-02) study and comparative (D-04) study groups and used in the linear regression analysis.

7.6.4-D. Responder Rate

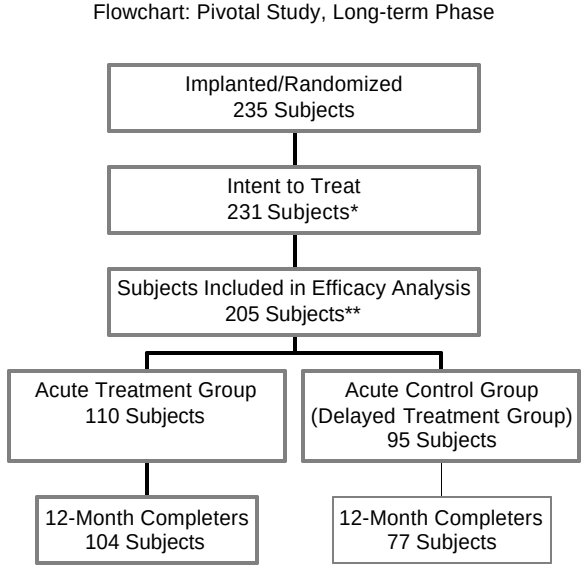
For each subject, the percentage of improvement in the assessment scores between baseline and post-treatment was calculated as follows.

{Mean Assessment Score (Visit B1 and Visit B2)-(assessment score at endpoint)} divided by Mean Assessment Score (Visit B1 and Visit B2) x 100

Response was defined as ?50% decrease in the endpoint score compared with the baseline score. Subjects with <50% reduction in the assessment were considered non-responders.

All statistical analyses were performed using the updated SAS version 8.2. All statistical tests were two-sided and performed at the 0.050 level of significance. No adjustments were made for multiple outcome measures.

Figure D-1. Pivotal Study, Long-Term



*4 subjects did not meet continuation criteria ($HRSD_{24}$ <18)
**Subjects not included in Efficacy Analysis
6 subjects: did not continue into long-term phase
20 subjects: not evaluable

7.7-D. Results

Figure D-1 provides a flow chart of subjects from the acute phase through the long-term phase of the pivotal (D-02) study. Information describing subjects in the pivotal (D-02) and comparative (D-04) studies is presented in Table D-7.

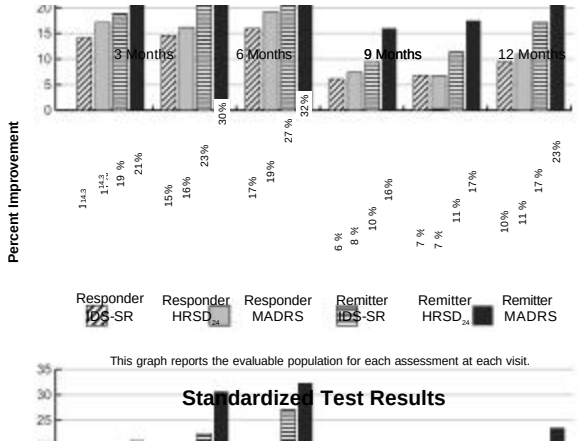
7.7.1-D. Results: Acute phase, pivotal (D-02) study

In the primary efficacy measure, $HRSD_{24}$ response rate, (the percentage of subjects achieving a ?50% improvement in $HRSD_{24}$ total score from baseline to acute phase exit), 15% of the treatment group and 10% of the sham-control group were responders (p=0.238). Analyses using a secondary efficacy parameter, the IDS-SR, did show a statistically significant advantage for VNS Therapy over sham treatment: 17% response versus 7% response (p=0.032) using the last observation carried forward (LOCF) method.

7.7.1.1-D. Consistent numerical trends supported VNS Therapy effectiveness

Although at 3 months the study did not show a statistically significant difference between the efficacy of VNS Therapy versus sham treatment in the population as defined by this study, the consistent numerical trends and occasional results of statistical significance on secondary outcome measures did provide supportive evidence of the effectiveness of VNS Therapy for subjects with treatment-resistant depression.

Figure D-2. Responder and Remitter Quarterly Results



7.7.2-D. Results: Long-Term Phase, Pivotal Study (D-02)

During long-term VNS Therapy, the D-02 subjects exhibited statistically significant and clinically meaningful improvement. The primary analysis found statistically significant improvement in $HRSD_{24}$ scores averaged over 12 months ($p<0.001$). Additionally, clinical significance was shown, using $HRSD_{24}$, in numbers and proportions of subjects achieving response (30%), remission (complete response; 17%). This improvement was consistent and seen across multiple assessments; the results of the IDS-SR, MADRS, and CGI corroborated the $HRSD_{24}$ analyses (Figure D-2, evaluable population, and Table D-8, 12-month completer population).

Table D-8. Responders, Remitters, and Percent Change Pivotal (D-02) Study 12-Month Completer Population

	HRSD$_{24}$[a]	IDS-SR[b]	MADRS
	12-Month Visit	12-Month Visit	12-Month Visit
Responders – N (%)			
Treatment	34/103 (33%)[2]	25/102 (25%)	34/103 (33%)[2]
Delayed treatment	18/71 (25%)	13/71 (18%)	22/71 (31%)[1]
All 12-Month Completers	52/174[a] (30%)[3]	38/173 (22%)[1]	56/174 (32%)[3]
Remitters – N (%)			
Treatment	19/103 (18%)[2]	16/102 (16%)[1]	25/103 (24%)[2]
Delayed treatment	10/71 (14%)	10/71 (14%)	16/71(23%)[1 c]
All 12-Month Completers	29/174 (17%)[2]	26/173 (15%)[2]	41/174 (24%)[3]
Percent Change			
Treatment	31.9% [3]	28% [3]	33% [3]
Delayed treatment	26.5% [3]	17% [3]	26% [3]
All 12-Month Completers	29.7% [3]	24% [3]	30% [3]

[1] $p<0.05$; [2] $p<0.01$; [3] $p<0.001$; Response and Remitter used the Exact McNemar's test compared with 3 months; Percent Change used the paired t-test (change from pre-stimulation baseline); Median percent change used the Wilcoxon Signed Rank test to determine whether the median was different from zero.

[a] Three subjects did not have 12-month HRSD$_{24}$ assessments. (These 3 subjects did have 11-month assessments).

[b] One subject did not have a baseline IDS-SR assessment and several others did not have 12-month assessments, which accounts for the varying Ns in the comparison of HRSD$_{24}$ with IDS-SR data.

[c] Two delayed-treatment subjects did not have 12-month MADRS assessments.

Treatment Group: Subjects who received VNS Therapy during the pivotal trial (D-02) acute phase

Control Group (Delayed Treatment Group): Subjects who received no VNS Therapy during the pivotal trial (D-02) acute phase, then began receiving VNS Therapy at the beginning of the pivotal trial (D-02) long-term phase

7.7.3-D. Improved Quality of Life

The observed improvement in depression among subjects in the pivotal (D-02) study long-term phase was supported by improved quality of life as measured by the MOS SF-36. Significant improvement was observed in several of the MOS SF-36 subscales: Vitality, Social Functioning, Role Functioning – Emotional, Mental Health ($p<0.01$), and the Physical and General Health Perceptions ($p<0.05$).

7.7.4-D. Tolerability - Subjects Continuing VNS Therapy at 12 months

Of the 295 subjects implanted during both the Feasibility (D-01) and pivotal Studies (D-02), 270 subjects (92%) were still receiving VNS Therapy after 12 months.

7.8-D. Results: Comparative (D-04) Study

The D-04 study provided a control group of similarly ill subjects who received usual standard-of-care therapies for 12 months but were not implanted with the VNS Therapy device. See Table D-7.

7.8.1-D. Well-Matched Populations

This comparison analyzed evaluable populations of 205 VNS Therapy subjects (D-02) and 124 usual standard-of-care subjects (D-04). Groups were well matched, with similar demographic, psychiatric, and mood disorder treatment histories. The only relevant significant differences between groups were in duration of current episode (with more months found in the D-04 group) and previous ECT history (with higher usage of ECT found in the D-02 group). These differences likely counter each other regarding the degree of treatment resistance of these two groups, and are handled within the efficacy analysis by use of a propensity adjustment. Clearly, the D-04 group was a similarly ill subject population.

7.8.2-D. Statistically Significant Improvement with Adjunctive VNS Therapy

The primary and secondary analyses comparing subjects treated with adjunctive VNS Therapy and usual standard of care (pivotal, D-02) with subjects treated with usual standard of care alone (comparative, D-04) showed that adjunctive VNS Therapy and usual standard of care produces statistically significantly greater improvement in depressive symptoms over 1 year of treatment. The primary efficacy analysis, a repeated measures linear regression analysis of the IDS-SR over 1 year, showed a statistically significant ($p<0.001$ evaluable; $p<0.001$ intent to treat) difference at a very robust level favoring adjunctive VNS Therapy and usual standard of care. (See Figure D-3.)

7.8.2.1-D. Secondary Analyses

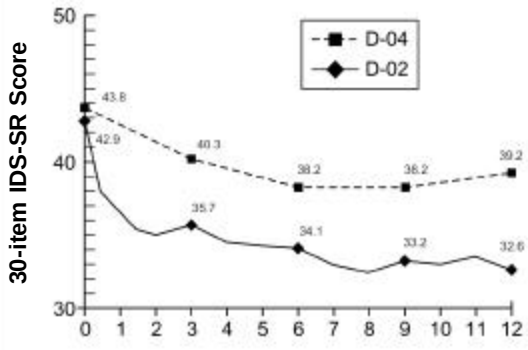
Additionally, essentially all secondary analyses were statistically significant and showed VNS Therapy improved

depressive symptoms more than usual standard-of-care after 12 months of therapy. IDS average change, IDS response, IDS complete response, IDS sustained response, $HRSD_{24}$ average change, and $HRSD_{24}$ response were all statistically significant. Last observation carried forward (LOCF) analyses supported the *a-priori* analyses.

7.8.3-D. Efficacy for Depressive Symptoms

These results indicate that adjunctive VNS Therapy provides significant benefit (efficacy) for depressive symptoms in a chronically ill or recurrent, treatment-resistant depression population, when compared with usual standard-of-care.

Figure D-3. Comparison of IDS-SR Scores of Pivotal Versus Comparative (D-04) Study Subjects by Study Visit



	Baseline	3 mon	6 mon	9 mon	12 mon
D-04	43.8 (N=124)	40.3 (N=120)	38.2 (N=119)	38.2 (N=116)	39.2 (N=112)
D-02	42.9 (N=205)	35.7 (N=203)	34.1 (N=191)	33.2 (N=183)	32.6 (N=180)

IDS-SR scores and number of subjects in pivotal (D-02) and comparative (D-04) studies by quarter

7.9-D. Efficacy Improved and Sustained Over Time

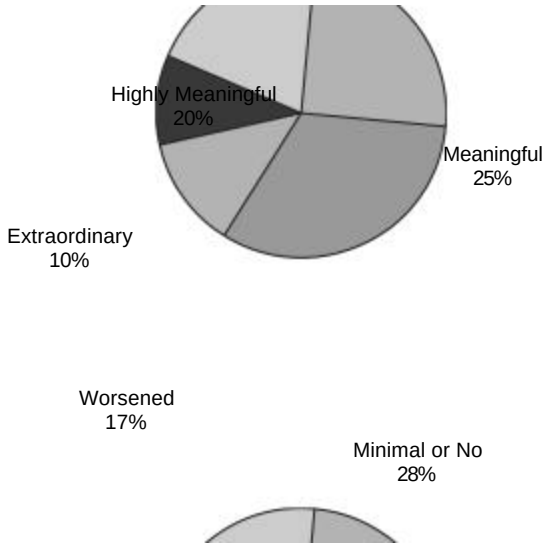
Subjects in the long-term phase of the pivotal (D-02) study continued to show improvement throughout 12-months of VNS Therapy (Figure D-3). At 12 months, 30% of subjects met criteria as responders or remitters, using $HRSD_{24}$, compared with 16% of subjects who were responders or remitters at 3 months. Although the regression models consistently indicated the greatest improvement during the first 3 months of treatment, proportions of subjects achieving response and remission at 12 months were consistently greater than at 3 months of treatment. For example, $HRSD_{24}$ scores improved 19.7% from 3 to 12 months of VNS Therapy. Additionally, when subjects were assigned to categories according to improvement, almost 50% of subjects who had no improvement at 3 months had some degree of benefit at 12 months of VNS Therapy.

7.10-D. Clinical Benefit Over Time

To explore whether these subjects were receiving benefit that was not fully reflected in the response rates, they were assigned to categories according to "clinical benefit." Clinical benefit was categorized as extraordinary (?75% improvement in $HRSD_{24}$), highly meaningful (50% to <75%), meaningful (25% to <50%), minimal (0% to <25%), and worsened (less than 0%). This scale is consistent with studies in many chronic illnesses that define less than a 50% improvement as a clinically meaningful response (eg, schizophrenia, obsessive compulsive disorder).

At 12 months of VNS Therapy, 30% of subjects experienced either an extraordinary or a highly meaningful clinical benefit and 25% had a meaningful benefit (55% had at least a meaningful benefit). This benefit was greater at 12 months compared with 3 months (Stuart-Maxwell test, $p<0.001$) (Figure D-4).

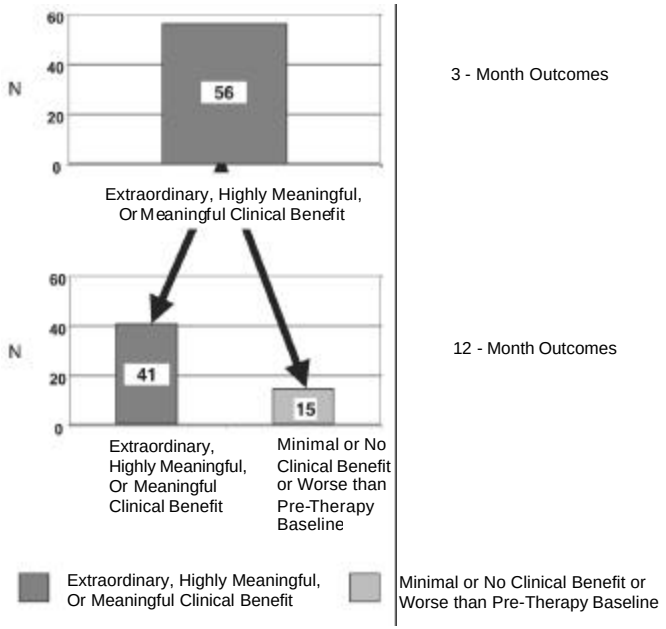
Figure D-4. Categories Identifying Degree of Clinical Benefit in D-02 ($HRSD_{24}$)
12-Month Completer Population (N=174)



The clinical benefit categorization can also be analyzed to further characterize benefit over time. Both those who had early benefit and those who did not were assessed later (12 months). Of the 56 subjects who had benefit at 3 months, 41 (73%) continued to have benefit at 12 months (Figure D-5).

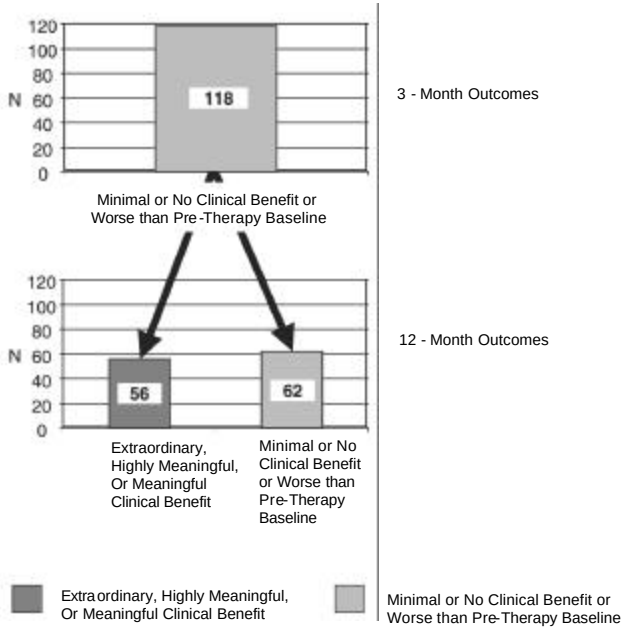
The results of this analysis show that most of the subjects in the pivotal (D-02) study maintained or increased their improvement: 34 of 56 subjects (61%) who exhibited extraordinary, highly meaningful or meaningful clinical benefit at 3 months of VNS Therapy exhibited the *same* or *more* improvement at 12 months of VNS Therapy. Of the 118 subjects who were without at least a meaningful benefit at 3 months, 56 (47%) had at least meaningful benefit at 12 months of VNS Therapy (Figure D-6). This indicates that a large portion of those who do not benefit early will receive meaningful benefit over time. More importantly for a treatment-resistant population, most subjects who have early meaningful benefit continue to maintain this meaningful benefit at 12 months.

Figure D-5. 12-Month Outcomes of Extraordinary, Highly Meaningful or Meaningful Clinical Benefit At 3 and 12 Months (N=56)



73% (41/56) of subjects maintained at least a meaningful benefit.

Figure D-6. 12-Month Outcomes of Pivotal (D-02) Subjects with Minimal or Less Clinical Benefit At 3 and 12 Months (N=118)



47% (56/118) of subjects with minimal or less benefit at 3 months of VNS Therapy obtained meaningful to extraordinary benefit at 12 months of VNS Therapy.

7.11-D. Antidepressant Treatments

Electroconvulsive therapy (ECT) use was similar among the pivotal (D-02) and comparative (D-04) subjects (7% and 6%, respectively).

7.11.1-D. Antidepressant Drugs and Response

Antidepressant drug use was greater among pivotal (D-02) study subjects who were non-responders and comparative (D-04) study subjects overall than among the pivotal (D-02) study subjects who achieved a response. During the 12 months, 77% of the pivotal (D-02) study non-responders and 81% of all comparative (D-04) study subjects either added a new antidepressant treatment or increased an existing antidepressant dose by an antidepressant resistance rating (ARR) level of one or more.

In contrast, only 56% of the pivotal (D-02) study subjects who were responders to VNS Therapy either added a new antidepressant treatment or increased an existing antidepressant dose by an antidepressant resistance rating (ARR) level of one or more.

Twice as many pivotal (D-02) study responders (44%) had no ARR changes or removed or decreased medications by at least one ARR level or were not taking medications as compared with non-responders (23%). These findings strongly support the conclusion that the VNS Therapy responders derived their benefit from VNS Therapy (or an augmentation effect of VNS Therapy) rather than from the concomitant antidepressant treatments.

Although medication changes were examined above and implied that medication changes in the subjects was not a consequential determinant of outcome, the possibility that only the D-02 subjects who showed improvement had *meaningful* medication sensitivity changes remains (though

highly improbable). To address this possibility an additional medication analysis was performed using the primary D-02 vs D-04 repeated measures linear regression methods. This approach uses a missing data paradigm to calculate the difference between the D-02 and D-04 groups that would have been observed under conditions where no inter-current changes in medications would have occurred in the D-02 group. This approach censors the D-02 IDS-SR scores after the point where a subject had a significant medication increase (ARR increase) or ECT treatment (all subsequent data points are carried forward and replace all subsequent non-missing IDS measurements). Therefore, all improvement for the D-02 group would be attributable to VNS Therapy alone and not to other treatment changes. Note that this approach is asymmetric, no censoring was performed on the D-04 data. Though this is a conservative approach, since D-04 treatment is akin to "best flexible medication (and/or ECT) management", it would be inappropriate to censor ratings after a treatment change. This extremely conservative analysis approached significance in the D-02 group as compared to D-04 ($p = 0.052$; 95% CI -0.37, 0.00) for the evaluable population.

7.12-D. ECT Versus VNS Therapy-Sustained Response

As a point of reference, the acute effect of ECT diminishes over time. A recent ECT study[5] shows that within 6 months of achieving remission (HRSD<=10), the relapse rate was 64%.

[5] Prudic J, Olfson M, Marcus SC, Fuller RB, Sackheim HA. The effectiveness of electroconvulsive therapy in community setting. *JAMA*. 2003 (in press).

Sackeim et al[6] reported that relapse after ECT response was almost twice as likely among patients who were medication-resistant: only 32% of such patients maintained their response during the year after ECT. The proportion of VNS Therapy-treated subjects maintaining their response compares favorably with that of patients who received ECT.

7.13-D. Benefits/Clinical Utility of VNS Therapy in the Treatment of Depression

Clinical trials supported the use of VNS Therapy as an adjunctive long-term treatment of chronic or recurrent depression for subjects experiencing a major depressive episode that had not had an adequate response to two or more adequate antidepressant treatments.

Expected results of adjunctive VNS Therapy for treatment-resistant depression

- a response (ie, at least a 50% improvement in depressive symptoms) in at least 15% to 17% of patients after 10 weeks of treatment
- a response in at least 21% to 37% of patients after 12 months of treatment
- remission (complete response) of depressive symptoms in at least 15% to 17% of patients after 12 months of treatment
- a sustained response in 13% to 27% of patients during 12 months of treatment
- successful maintenance of the initial improvement in a high percentage of patients (eg, 73% to 77% of patients

[6] Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized,double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry.* 2000;57:425-434.

who had meaningful or greater benefit at 3 months of treatment maintained at least meaningful benefit after 12 months of treatment)

Benefits of non-systemic mechanism of action

- a very well-tolerated therapy as indicated by the high continuation rate for therapy after 12 months (92%)
- adverse effects essentially limited to those related to stimulation of the vagus nerve, ie, an absence of the systemic effects associated with drug therapy; many of the common adverse effects only occur when stimulation of the vagus nerve is actually occurring
- the ability to halt acute stimulation-related adverse effects immediately through the use of magnet deactivation of stimulation
- an absence of adverse cognitive and psychomotor effects
- an absence of overdose toxicity
- favorable findings in animal reproductive studies
- ability to add VNS Therapy to antidepressant drug therapy without producing drug-drug interactions
- assured compliance with the ability to turn off stimulation to control side effects, if desired, because VNS Therapy is programmed to work automatically without the need for patient action (ie, no pills to take)

7.14-D. Bibliography

A bibliography of animal and clinical studies is available from Cyberonics on request.

8-D. INDIVIDUALIZATION OF TREATMENT

Patients should be started on stimulation at a low current output setting (0.25 mA), and the current should be increased gradually to allow accommodation to the stimulation. For patient comfort, the output current should be increased in 0.25 mA increments until a comfortable tolerance level is reached. Physicians should appreciate that some patients will accommodate to stimulation levels over time and should therefore allow further increases (in 0.25 mA steps) in output current, if needed. (See the Model 250 Software Physician's Manual.)

Table D-9 lists the stimulation parameters reported at 12 months of VNS Therapy in the pivotal (D-02) study.

Table D-9. Stimulation Parameters at 12 months of VNS Therapy in the pivotal (D-02) study

Stimulation Parameters	Median Value at 12 months	Range
Output current	1.0	0 to 2.25
Frequency	20 Hz	2 to 30 Hz
Pulse width	500 ?sec?	130 to 750 ?sec
ON time	30 sec	7 to 60 sec
OFF time	5 min	0.3 to 180 min

The magnet output current should be set to 0 mA.

⚠ The safety and efficacy of this therapy have not been systematically established for uses not covered in the "Intended Use / Indications" section of this manual or in patients with the following conditions:

- Cardiac arrhythmias or other abnormalities
- History of dysautonomias
- History of previous therapeutic brain surgery
- History of respiratory diseases or disorders, including dyspnea and asthma
- History of ulcers (gastric, duodenal, or other)
- History of vasovagal syncope
- Neurological diseases other than epilepsy or depression
- Only one vagus nerve
- Other concurrent forms of brain stimulation
- Pre-existing hoarseness
- Pregnancy or nursing*

*Pre-clinical Study, Teratogenic Effects: There are no adequate and well-controlled studies of VNS Therapy in pregnant women. Reproduction studies have been performed using female rabbits stimulated with the commercially available VNS Therapy System at stimulation dose settings similar to those used for humans. These animal studies have revealed no evidence of impaired fertility or harm to the fetus due to VNS Therapy. Because animal reproduction studies are not always predictive of human response and animal studies cannot address developmental abnormalities, VNS should be used during pregnancy only if clearly needed. Although the operating ranges of the VNS Therapy System and fetal monitors are dissimilar and no interaction would be expected, testing has not been performed. Therefore, the potential may exist for interaction between the VNS Therapy System and fetal monitoring systems.

9-D. PATIENT COUNSELING INFORMATION

In the unlikely event of uncomfortable adverse events, continuous stimulation, or other malfunction, the patient must be advised to hold or tape the magnet directly over the implanted Pulse Generator to prevent additional stimulation. If patients or caregivers find this procedure necessary, they should immediately notify the patient's physician.

10-D. CONFORMANCE TO STANDARDS

The VNS Therapy System conforms to the following standards:

- American National Standards Institute (ANSI) and Association for the Advancement of Medical Instrumentation (AAMI) NS15 — Implantable, peripheral nerve stimulators
- EN 45502-1 — Active Implantable Medical Devices: Requirements for the safety, marking, and information to be provided by the manufacturer

11-D. HOW SUPPLIED

Implantable portions of the VNS Therapy System have been sterilized using ethylene oxide gas (EO), and are supplied in a sterile package for direct introduction into the operating field. A process indicator is included in the package; devices should be implanted only if the indicator is green. An expiration date is marked on the outer package.

If the package has been exposed to extreme temperatures or moisture (see Section 5.1 in the epilepsy part of this manual) or if there is any indication of external damage, the package should be left unopened and returned to Cyberonics.

12-D. OPERATOR'S MANUAL

12.1-D. Directions for Use

Please refer to Section 12.1 in the epilepsy part of this manual. The Directions for Use are equivalent for epilepsy and depression with the following exceptions.

- For patients with depression, the Magnet Mode output current should always be programmed at 0.0 mA, the setting at which the Pulse Generator is shipped from Cyberonics.
- Use of the Magnet Mode is limited to patients with epilepsy. Patients with epilepsy or their caregivers pass the magnet over the implanted Pulse Generator to activate on-demand delivery of a single train of vagus nerve stimulation and help abort or diminish a seizure.
- Magnet Mode is not used for patients with depression.

12.2-D. Physician Training/Information

Please refer to Section 12.2 in the epilepsy part of this manual.

12.3-D. Mechanism of Action

Studies examining the central nervous system effects of vagus nerve stimulation contributed to the rationale for VNS Therapy's use as an antidepressant. Given the known projections of the vagus nerve within the brain and preliminary work examining the effect of vagus nerve stimulation on neurotransmitters, it seems that stimulating the vagus nerve produces effects on norepinephrine and serotonin,

the two principal neurotransmitters implicated in the therapeutic effect of antidepressant drugs.[7]

Additionally, neuroimaging studies show that VNS Therapy modulates activity in regions of the brain believed to be involved in mood regulation, including limbic structures and specific cortical areas such as the orbitofrontal cortex. Finally, Kral recently demonstrated that VNS Therapy produces effects in the rat forced swim test (FST) paradigm that are comparable to those of the tricyclic antidepressant drug desipramine. The FST is a behavioral model commonly used to identify potential antidepressant drugs.

Harden[8] and Elger[9] both reported improvements in the depression scores of patients receiving VNS Therapy for the treatment of epilepsy based on the use of standardized depression rating scales. These improvements were not dependent on improvement in the patients' seizures, and provided a basis for further investigation into the antidepressant role of VNS Therapy.

12.4-D. Detailed Device Description

Please refer to Section 12.4 in the epilepsy part of this manual for a detailed device description.

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[7] Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression, part 3: psychosocial functioning bef ore and after treatment with sertraline or imipramine. *J Clin Psychiatry.*1998;59:608-619.

[8] Harden CL, Pulver MC, Ravdin LD, et al. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. *Epilepsy Behav.* 2000;1:93-99.

[9] Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res.* 2000;42:203-210.

13-D. CYBERONICS' LIMITED REPLACEMENT WARRANTY

Please refer to Section 13 in the epilepsy part of this manual.

14-D. TROUBLESHOOTING

Please refer to Section 14 in the epilepsy part of this manual for assistance in troubleshooting the VNS Therapy System.

15-D. INFORMATION AND SUPPORT

If there are questions regarding use of the VNS Therapy System or any of its accessories, please contact Cyberonics:

USA

Cyberonics, Inc.
100 Cyberonics Boulevard
Houston, Texas 77058

Telephone: (281) 228-7200
Fax: (281) 218-9332

For 24-hour support, please call:

Telephone: (800) 332-1375	General Operator
Ext 7330	Technical Support
Ext 7337	Clinical Support

Europe

Cyberonics Europe, S.A.
Belgicastraat 9
1930 Zaventem
Belgium

Telephone: 32 2 720 95 93
Fax: 32 2 720 60 53

Internet

www.cyberonics.com

16-D. GLOSSARY

ACLS	Advanced Cardiac Life Support
AE (Adverse Event)	Any symptom, sign, illness, or experience that develops or worsens in severity and/or frequency during the course of the study (ie, any changes from baseline)
ARR	Antidepressant Resistance Rating
Baseline Periods	
D-02 Acute Phase	Two pre-implantation visits (Visits B1 and B2) for both groups
D-02 Long-Term Phase	For the evaluation of efficacy, the period just before initiation of VNS Therapy; during the long-term phase, the baseline period of subjects who had been assigned to the acute treatment group during the acute phase differed from that of the subjects who had been assigned to the acute sham-control group; because this baseline period is just before treatment initiation for both groups, it is more comparable for analysis purposes

Treatment Group	During the long-term phase, the baseline for the subjects who had been assigned to the acute treatment group during the acute phase was the pre-implantation baseline (B1 & B2)
Delayed Treatment Group (Acute Sham-control Group)	During the long-term phase, the baseline for the subjects who had been assigned to the acute sham-control group during the acute phase was the final two acute study visits, V8 and V9 (acute study exit)
D-04	The visit occurring after obtaining informed consent
BOL	Beginning of Life

CGI (Clinical Global Impression)	Two 7-point scales completed by the clinical rater to assess the subject's condition regarding the severity of illness (CGI-S) and global improvement (CGI-I); the severity scale ranges from 1 – "normal, not at all ill" to 7 – "among the most extremely ill patients;" the improvement scale ranges from 1 – "very much improved" to 7 – "very much worse;" the CGI was developed by the NIMH to provide a standardized assessment with clinically relevant anchors; it is one of most widely used brief assessment tools in psychiatry.
Chronic or Recurrent Depression	A current major depressive episode that is of at least two years in duration or a current major depressive episode in a patient with a history of multiple prior episodes of depression.

Clinical Benefit	Degree of improvement in depression as measured by the $HRSD_{24}$; physician expert consultants to the Sponsor developed this designation ? ? extraordinary clinical benefit, at least a 75% reduction from baseline ? ? highly meaningful clinical benefit, at least a 50% but less than a 75% reduction from baseline ? ? meaningful clinical benefit, at least a 25% but less than a 50% reduction from baseline ? ? minimal or no clinical benefit, at least no change or less than a 25% reduction from baseline ? ? worsened: increase in $HRDS_{24}$ compared with baseline
Complete Response (Complete Responder or Remitter)	Subjects who scored less than a pre-defined score were considered to have achieved a complete response; scores representing complete response were an $HRSD_{24}$ raw score of 9 or less, a MADRS raw score of 10 or less, or an IDS-SR raw score of 14 or less; this corresponds to the concept of remission, where the illness, in this case depression, has few to no residual symptoms present

Duty Cycle	Percentage of time during which stimulation occurs; stimulation time (programmed ON time plus 2 seconds of ramp-up time and 2 seconds of ramp-down time) divided by the sum of signal ON and OFF times
EAS	Electronic article surveillance
ECT (Electroconvulsive Therapy)	A treatment for depression and other indications using electrodes on the surface of the head to direct electrical current into the brain to induce generalized seizures in a patient
EMI	Electromagnetic interference
EOS	End of service
ERI	Elective replacement indicator
Excess Duty Cycle	Duty cycle for which the ON time is greater than the OFF time
Failed Adequate Treatment	Failure to respond to electroconvulsive therapy or an established antidepressant drug administered at an adequate dose for an adequate duration.
FDA	United States Food and Drug Administration

HRSD (Hamilton Rating Scale for Depression)	The HRSD is the most widely used rating scale to assess symptoms of depression; a multi-dimensional, observer-rated scale for assessing overall depression severity; the 28-item version of the scale was administered to subjects in this study; per protocol for the feasibility (D-01) study, all 28 items were used for rating purposes; per protocol for the pivotal (D-02) study, only the first 24 items were used for rating purposes
High Lead Impedance	DC-DC Converter Codes greater than four on a device diagnostic test; not a sole determinant of a need for Lead replacement
IDS-SR (Inventory of Depressive Symptomatology Self-Report)	A 30-item patient self-report rating of the symptoms of mood and depression; this validated scale is becoming more widely used in clinical studies for assessing depression symptoms
LIMIT Output Current	Output current other than that which was programmed; not a sole indicator of a device malfunction
LOCF (Last Observation Carried Forward)	This analysis technique uses the last available data point for subsequent time points where data is missing

Long-term Phase	The portion of the pivotal (D-02) study comprising follow-up after the acute portion of the study (after Visit 9); the long-term portion included longitudinal follow-up by a blinded rater; the analysis of the long-term data included a repeated measures within-subjects analysis of changes in depressive symptoms at 12 months of VNS Therapy
MADRS (Montgomery Asberg Depression Rating Scale)	A 10-item scale completed by the clinical rater for assessing overall depression severity; this rating scale is common in Europe
Magnet Activation	Brief magnet application and removal, which initiates a stimulation
Microcoulomb	Product of current and time, or output current (in mA) multiplied by the pulse width (in msec)
MOS SF-36 (Medical Outcome Survey 36-Item Short Form Health Survey)	A quality of life (QOL) tool that assesses overall QOL and subscales of physical functioning, role functioning-physical, bodily pain, general health perceptions, vitality, social functioning, role functioning-emotional, mental health, and overall change in health

Nominal Parameters	Specific preset parameters available with the software; Cyberonics suggests that the Pulse Generator be set to these parameters when patients are first stimulated (see Section 12.1.1 in the epilepsy part of this manual for specific nominal parameters)
Output Current	Amount of electrical current delivered in a single pulse of a stimulation, measured in mA
Patient Code	Any three-digit combination assigned by the treating physician; generally programmed at time of implantation; often patient's initials: first, middle, last (or with a hyphen for no known middle initial)
Pulse Width	Duration of a single pulse within a stimulation, measured in ?sec
Ramp-down	Gradual decrease over approximately 2 seconds in output current at the end of stimulation greater than 10 Hz in signal frequency
Ramp-up	Gradual increase over approximately 2 seconds in output current at the beginning of stimulation greater than 10 Hz in signal frequency

Refractory	Resistant to previous treatment alternatives defined by the treating physician; generally refers to the depressive symptoms of patients who have tried and failed two or more antidepressant treatments
Remission (Remitter)	See Complete Response
Reset Parameters	Parameters to which the Pulse Generator internally programs when it is reset (see Section 12.1.1 in the epilepsy part of this manual for specific reset parameters)
Responder	At a given point, a subject with a ?50% reduction in HRSD, MADRS, or IDS-SR scores at 12 months of stimulation compared with baseline (see Baseline Period definition)
Response (Responder)	A subject with at least a 50% reduction in depression assessment (ie, $HRSD_{24}$, MADRS, or IDS-SR) compared with the baseline

SAE (Serious Adverse Event)	Any adverse event that resulted in any of the following outcomes: death, a life threatening adverse experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect or any medical intervention that prevents one of the above; the sponsor also included cancer and pregnancy as SAEs
Signal Frequency	Repetition rate of pulses in a stimulation; measured in number of pulses per second (Hz)
Signal OFF Time	Interval between stimulations when there is no stimulation; measured in minutes
Signal ON Time	Length of time the programmed output current is delivered (not including ramp-up and ramp-down times); measured in seconds
Statistically Significant	Results are considered statistically significant if p-values for the appropriate statistical tests are less than or equal to 0.050

Stimulation Adjustment Period	For the treatment group, a 2-week period between Visit 2 and Visit 4 during the acute portion of the study. For the delayed treatment group, a 2-week period between Visit 9 and Visit 11 at the start of the long-term study. The output current was progressively increased to a comfortably tolerable level during this period. After this period, output current was held constant for an 8-week period unless reduction was necessary for tolerance
Stimulation Parameters	Programmed output current, signal frequency, pulse width, signal ON time, and signal OFF time
Stimulation Time	Therapeutic output of the VNS Therapy Pulse Generator; consists of the signal ON time, plus 2 seconds of ramp-up time and 2 seconds of ramp-down time
Treatment-Emergent	Adverse events that occurred on or after the implant and were not present during the baseline period or events that were present during baseline that worsened in severity after the implant

Treatment Failures	Subjects who, after the randomization procedure, 1) exited the acute study before Visit 9 due to treatment-related adverse events, or a lack of efficacy 2) met the suicide exclusion criteria, 3) attempted suicide resulting in hospitalization of more than 3 days, or 4) developed mania or more than three mood episodes as defined by DSM-IV. Subjects who were treatment failures during the acute study were also considered treatment failures for long-term analysis purposes
UADE (Unanticipated Adverse Device Effect)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application); also, any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients
Vagus Nerve	Either of the pair of tenth cranial nerves arising from the medulla and supplying mainly the viscera, especially with autonomic sensory and motor fibers; in this document, vagus nerve always refers to the *left* vagus nerve

VNS	Vagus Nerve Stimulation
VNS Therapy™	VNS delivered by Cyberonics' Neurocybernetic Prosthesis
Within-Group	A statistical comparison including only subjects in the same group assignment
YMRS (Young Mania Rating Scale)	An 11-item scale completed by the clinical rater to assess the symptoms of mania